# A Comparison of Laparoscopic with Open Distal Gastrectomy in Advanced Gastric Cancer after Neoadjuvant Chemotherapy (REALIZATION Trial)

Study Protocol

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## Summary

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|---|---|
| Title | A Comparison of Laparoscopic with Open Distal Gastrectomy in Advanced Gastric Cancer after Neoadjuvant Chemotherapy |
| Objectives | To determine the non-inferiority of laparoscopic distal gastrectomy (experimental group) compared with open distal gastrectomy (control group) on 3-year recurrence-free survival for patients with preoperative clinical stage of locally advanced gastric cancer receiving neoadjuvant chemotherapy |
| Design | Phase II, single-center, open-label, non-inferiority, randomized controlled trial |
| Outcomes | Primary Outcome: 3-year progression-free survival<br>Secondary Outcomes: 3-year overall survival, surgical radicality, surgical morbidity, surgical mortality, postoperative recovery index, postoperative quality of life |
| Study Duration | 5 years |
| Interventions | Group A (experimental group): laparoscopic distal gastrectomy with D2 lymphadenectomy<br>Group B (control group): open distal gastrectomy with D2 lymphadenectomy |
| Number of Subjects | 96 |
| Population | Patients with locally advanced gastric adenocarcinoma receiving neoadjuvant chemotherapy |

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## 1. Background

### 1.1. Epidemiology of Gastric Cancer

Gastric cancer is the fourth most common malignant tumors and the second leading cause of cancer death worldwide.[1] Although the incidence of gastric cancer is slightly declining in the past half century worldwide, it persists at a high level in East Asia. China carries the heaviest burden of gastric cancer, as almost half of gastric cancer cases occur in China.[1, 2] Moreover, due to the difficulty of screening and early diagnosis, approximately 80% of gastric cancer patients in China are already at advanced stage at first hospital visit.

### 1.2. Treatment of Gastric Cancer

The established treatment for advanced gastric cancer is open gastrectomy with D2 lymph node dissection and postoperative adjuvant chemotherapy of S-1 for one year or combination therapy with capecitabine and oxaliplatin for six months.[3] Though such a treatment regimen is effective, the prognosis of patients is not satisfactory, which calls for a more intensive chemotherapy. From theoretical perspectives, an intensified chemotherapy can be better tolerated and complied by patients if being administered before the surgery. By far, two large European phase III trials, the MAGIC and the FNCLCC/FFCD, have provided supportive evidence that preoperative (neoadjuvant) chemotherapy results in high compliance as well as other favorable factors such as high rate of R0 resection and tumor regression that lead to a better prognosis.[4, 5]

Laparoscopic gastrectomy has been used as an alternative to open gastrectomy to treat early gastric cancer. Though still in debate, the application of laparoscopic surgery in advanced gastric cancer has drawn increasing attention over the years. There have been a number of randomized trials comparing laparoscopic with open gastrectomy,[6] but very few on this comparison after neoadjuvant chemotherapy. To our best knowledge, only one similar trial was proposed to be carried out from 2011 to 2014 in Japan but results have yet been published.[7] Such a trial is worthwhile for the following two reasons. On one hand, laparoscopic gastrectomy is considered to be more technically difficult than open gastrectomy due to the complex structures of blood vessels and lymphatic drainages around the stomach, and neoadjuvant chemotherapy may increase these difficulties by inducing fibrotic changes of tissues and the destruction of anatomical dissection plane. On the other hand, laparoscopic surgery has certain advantages over open surgery, manifesting as the visual magnification, better exposure, and more delicate maneuvers of organs, vessels, and nerves.

### 1.3. Necessity and Novelty of Current Study

- The neoadjuvant chemotherapy and laparoscopic treatment of advanced gastric cancer are the current research hotspots.
- There is no high-level evidence on safety and efficacy of laparoscopic gastrectomy as compared to traditional open gastrectomy after neoadjuvant chemotherapy domestically and internationally.
- The uniquely very large burden of advanced gastric cancer in China warrants the necessity and urgency of studies which may have a significant impact on the prognosis and life quality of gastric cancer patients in China.

## 2. Objectives

### 2.1. Primary Objective

- To determine the non-inferiority of laparoscopic distal gastrectomy after neoadjuvant chemotherapy compared with open distal gastrectomy after neoadjuvant chemotherapy on 3-year recurrence-free survival for patients with preoperative clinical stage of locally advanced gastric cancer

### 2.2. Secondary Objectives

- To compare 3-year overall survival rate of laparoscopic distal gastrectomy to open distal gastrectomy after neoadjuvant chemotherapy
- To compare surgical radicality of laparoscopic distal gastrectomy to open distal gastrectomy after neoadjuvant chemotherapy
- To compare perioperative safety of laparoscopic distal gastrectomy to open distal gastrectomy after neoadjuvant chemotherapy
- To compare operative trauma and early postoperative recovery of laparoscopic distal gastrectomy to open distal gastrectomy after neoadjuvant chemotherapy
- To compare postoperative 1-year quality of life of laparoscopic distal gastrectomy to open distal gastrectomy after neoadjuvant chemotherapy

## 3. Overall Design

### 3.1. Study Site

The study took place in the Gastrointestinal Cancer Center of Peking University Cancer Hospital in China.

### 3.2. Control Group and Grouping

Group A (experimental group): laparoscopic distal gastrectomy with D2 lymphadenectomy

Group B (control group): open distal gastrectomy with D2 lymphadenectomy

### 3.3. Sample Size Estimate

A double-criteria approach described in the paper of Neuenschwander et al was used to calculate the required sample size in order to identify non-inferiority of laparoscopic versus open gastrectomy in terms of 3-year recurrence-free survival.[8] The first criterion was that the point estimate of hazard ratio comparing laparoscopic to open gastrectomy was smaller than a critical threshold of 1.12. The second criterion required that the upper limit of confidence interval of the hazard ratio was smaller than the non-inferiority margin of 1.59. These two thresholds are selected on the basis of clinical consideration and previous literature. On the basis of this approach, a sample size of 80 (40 per arm) is planned, with a type I error of 0.05 (one-sided). The total sample size is 96 (48 per am) after taking account of a 20% dropout rate in each group.

From a Bayesian perspective, this sample size enables that, when declaring non-inferiority, we have 95% or more certainty that the true difference is better than the non-inferiority margin (aka. 1.59) and that the Level of Proof for the critical value is 0.5.

Non-inferiority will be declared if the point estimate of hazard ratio comparing laparoscopic to open gastrectomy is smaller than 1.12 and that the upper limit of one-sided 97.5% confidence interval is smaller than 1.59.

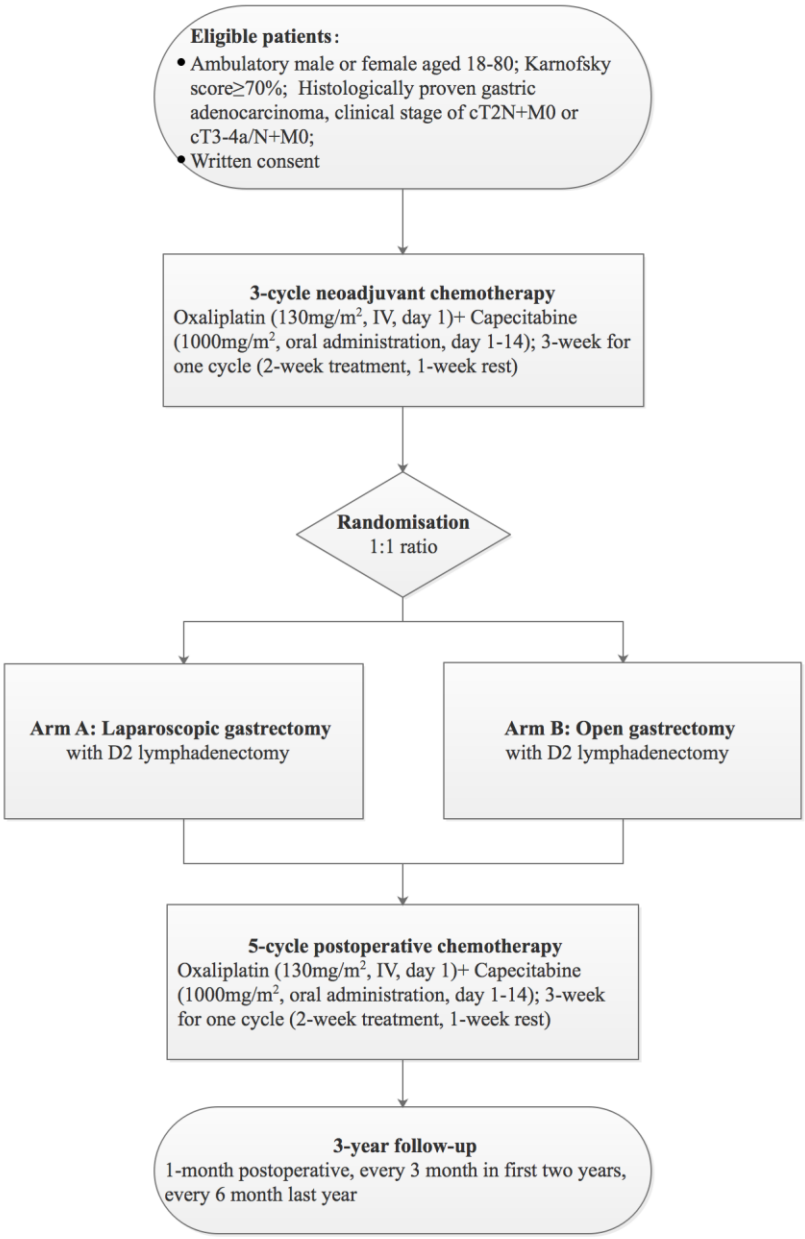
### 3.4. Randomization, Allocation Concealment, and Blinding

In three weeks after the last cycle of neoadjuvant chemotherapy, patients with resectable tumor will be randomized to receive either laparoscopic gastrectomy with D2 lymph node dissection or open gastrectomy with D2 lymph node dissection in a 1:1 ratio. The data manager, who is separate from the eligibility assessment and recruitment of patients, will do the randomization using a list of randomly ordered treatment identifiers generated by a permuted block design with SAS version 9.4 (SAS Institute, Cary NC). The allocation sequence is concealed from the surgeons who enroll patients until patients have been formally assigned to their groups. While it is not feasible to blind surgeons and participants, pathologists and radiologists are unaware of the treatment received by the patients.

### 3.5. Study Period

- Patient Enrollment: the plan is to complete the enrollment within 2 years.
- Follow-up period: The enrollment of the first case is used as the starting point of the follow-up, and 3 years after the last case is included as the end point of follow-up.

### 3.6. Study Flowchart




## 4. Research subjects

### 4.1. Inclusion Criteria

- Ambulatory male or female aged to 18 to 80
- Karnofsky score≥70%
- Histologically proven gastric adenocarcinoma in biopsy (including Lauren classification)
- Proven clinical stage of cT2N+M0 or cT3-4a/N+M0 by baseline ultrasound endoscope, enhanced CT/MRI examination using Habermann Standards, or diagnostic laparoscopy.

- No past chemotherapy or radiotherapy before diagnosis
- Primary tumor located at middle or lower stomach, achievable naked-eye complete resection (R0/1) via distal subtotal or total gastrectomy plus lymphadenectomy
- Haematology and biochemistry index meet the following: hemoglobin≥80g/L, absolute neutrophils count (ANC)≥1.5×109/L, platelet≥100×109/L, ALT、AST≤2.5 times the upper limit of normal value, ALP≤2.5 times the upper limit of normal value, serum total bilirubin<1.5 times the upper limit of normal value, serum creatinine<1 times the upper limit of normal value, serum albumin≥30g/L
- No severe concomitant disease that leads to survival<5 years
- Willing and able to comply with study protocol
- Written agreement consent before enrolment and full awareness of the right to quit the study at any time with no loss

**4.2. Exclusion Criteria**

- Pregnant or breastfeeding;
- Uncontrolled seizure, central nervous system diseases or mental disorders;
- History of upper abdominal surgery (except for laparoscopic cholecystectomy);
- History of gastric surgery (including diagnosis procedure such as endoscopic submucosal dissection and endoscopic mucosal resection);
- Other malignant diseases in 5 years (except for cured skin carcinoma and cervical carcinoma in situ);
- Clinically severe or active heart diseases, such as symptomatic coronary heart disease, the New York Heart Association (NYHA) grade II or above congestive heart failure, severe arrhythmia, or myocardial infarction in 6 months;
- Cerebral haemorrhage or infarction in 6 months;
- Organ transplant recipient under immunosuppressive therapy;
- Severe uncontrolled repeated infection or other severe uncontrolled concomitant diseases;
- Medium or severe renal damage (creatinine clearance rate ≤50ml/min or serum creatinine greater than the upper limit of normal value);
- Other diseases requiring synchronous surgery; requiring emergent surgery due to oncological emergency (eg, bleeding, perforation, obstruction);

- Forced expiratory volume in 1s <50% of expected value; and participated in other studies 4 weeks before the randomisation.

**4.3. Withdrawal Criteria**

Subjects have the right to withdraw from the study at any time during the trial, or to terminate the study early if:

- Clinical evaluation after neoadjuvant chemotherapy is progression disease (PD), which is not suitable for surgical treatment.
    - Patients who are diagnosed with PD during treatment must discontinue the treatment of the study. The post-progress treatment is determined by a multidisciplinary discussion organized by the investigators and must be documented in the CRF.
    - One of the following conditions will be considered as PD:
        - There is evidence that the patient has developed a new metastatic lesion,
        - There is evidence to confirm that the patient's original lesion has progressed,
        - Death has occurred for any reason.

    Note: New metastatic lesions should be confirmed by cytology or histology. Without the support of other objective indicators (ie, radiology, histology/cytology), elevated level of tumor markers alone or unexplained clinical deterioration cannot be used as a basis for a diagnosis of progression. The date of progression is defined as the date on which an objective test yields a positive result.
- Metastatic gastric cancer (M1) confirmed during or after surgery.
- T4b or a tumor that invades the duodenum confirmed during or after surgery.
- Presence of regional fusion of lymph nodes confirmed intraoperatively which cannot ensure R0 resection or surround important vessels and cannot be dissected.
- Intraoperative confirmed total gastrectomy is required to ensure adequate proximal margin.
- Sudden comorbidities before surgery so that surgery or anesthesia cannot be tolerated and the study protocol cannot be followed.
- Those who need emergency surgery due to changes in the patient's condition after enrollment.
- The subject or subject's legally authorized representative requests to withdraw from the study.

- Determined after the enrollment that the subject does not meet the inclusion and exclusion criteria.
- Lost to follow-up or non-compliance.
- Unfit to continue the study due to adverse events.

For subjects who withdraw from the study, the reason for the early withdrawal should be recorded, and the time of the last medication/intervention of the study should be recorded, and the examination items should be completed in the last visit as much as possible.

**4.4. Recruitment of Cases**

Before the screening visit, the patient's instructions are sent to the patient and the patient is given a certain amount of time to read all the instructions, communicate with the investigators on relevant circumstances or ask questions. During the screening visit, the patient should be verbally informed about the research content and specific operations involved. Patients must sign and date the informed consent form approved by the appropriate ethics committee before the selection process begins.

**4.5. Selection of Cases**

During the screening period, the investigator will firstly provide written informed consent for and explain the content in detail to the subjects who may be included in the study. When the subject signs the informed consent form, the investigator will assign a screening identification number based on the time at which the subject signs the informed consent form. Signing this informed consent indicates that the patient has entered the study and can be screened according to the following items:

- Demographic data;
- Medical history taken within 2 weeks prior to the screening process, including at least the history of gastric cancer and related treatment, as well as concomitant diseases and relevant treatment;
- Urine pregnancy test (fetal females, if applicable) performed within 1 week prior to the screening process;
- Vital signs examination performed within 1 week prior to the screening process, including blood pressure (in sitting position), heart rate, respiratory rhythm, and body temperature (underarm);
- Physical examinations (height, weight, Karnofsky score, heart/lung/abdominal routine physical examination) performed within 1 week prior to the screening process;

- Laboratory examinations performed within 1 week prior to the screening process (fasting blood should be required; for hemodialysis patients, blood should be taken before dialysis), including:
  - Blood cell analysis should include at least: WBC, LYM, NEU, NEU%, RBC, Hb, PLT
  - Blood biochemical analysis should include at least: albumin, AST, ALT, total bilirubin, creatinine, urea nitrogen, fasting blood glucose, CRP
- Tumor evaluations performed within 4 weeks prior to the screening process, including:
  - Abdominal enhanced CT and / or MRI scan
  - Endoscopic ultrasound
  - Chest plain scan CT
  - Cervical lymph node ultrasound
  - Pelvic ultrasound / CT
  - Serum tumor markers, including at least: CEA, CA199, CA724, CA242, CA125
  - Laparoscopic exploration and abdominal cytology
- 12-lead ECG under calm conditions within 2 weeks prior to the screening process
- Respiratory function tests performed within 2 weeks prior to the screening process, including at least: FEV1, FVC

### 4.6. Enrollment of Cases

After the subject completes all screening tests and were determined to meet the inclusion/exclusion criteria, the subject will receive a subject identification number. Screened test results can be accepted as baseline characteristics.

## 5. Endpoint

### 5.1. Primary Endpoint

- 3-year progression-free survival: defined as time from the day of surgery to the date of tumor recurrence (local, regional, or distant), all-cause death, or last follow-up, whatever occurs first.

### 5.2. Secondary Endpoints

- 3-year overall survival: defined as time from the day of surgery to the date of all-cause death or last follow-up, whatever occurs first.

- Surgical radicality: defined as the degree to which the gastrectomy is radical. The evaluation includes assessments on the number of lymph nodes retrieved, the state of resection margin, and R0 resection rate.
- Surgical morbidity: defined as postoperative complications occurring within 30 days after surgery and will be classified according to the Clavien-Dindo classification system. Postoperative complications include incision complications (infection, effusion, rupture, poor healing), ascites or abscess formation, hemorrhage (intraperitoneal, digestive tract), intestinal obstruction, anastomotic leakage, anastomotic stenosis, intestinal fistula, lymphatic leakage, pancreas fistula, gastroparesis, pancreatitis, pulmonary infection, pleural effusion, urinary tract infection, renal failure, liver failure, cardiovascular and cerebrovascular events (double lower extremity thrombosis, pulmonary embolism, myocardial infarction, arrhythmia, cerebral infarction, etc.), and others.
- Surgical mortality: defined as death occurring within 30 days after surgery, regardless of the cause.
- Postoperative recovery index: includes postoperative blood transfusion, postoperative pain score and dosage of analgesics, first time of ambulation, first aerofluxus time, first defecating time, first time on a liquid diet, time of gastric tube and drainage removal, and length of hospital stay. Postoperative pain intensity is measured by using a Visual Analogue Scale up to 72 hours after surgery. Dosage of analgesics is measured as the time of applying intravenous patient-controlled analgesia and rescue morphine consumption.
- 1-year postoperative quality of life: assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaires (QLQ- C30 and QLQ-STO22). Patients will complete both C30 and STO22 within 7 days before the treatment, within 7 days after the treatment, at 12 months after surgery. The EORTC-C30 instrument includes 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, pain and nausea, and vomiting), 1 global health status, and 6 single items.

## 6. Preoperative neoadjuvant chemotherapy

### 6.1. Preoperative neoadjuvant chemotherapy program

Patients will first receive neoadjuvant chemotherapy with oxaliplatin plus capecitabine as follows:

- Oxaliplatin: 130mg/$m^2$, 2 hours intravenous drip, day 1;

- Capecitabine: 1000mg/$m^2$, oral administration within 30 minutes after meal, Bid, days 1-14; treatment for 2 weeks, rest for 1 week
- Repeat every 3 weeks for a total of 3 cycles.

**6.2. Safety evaluation indicators of preoperative neoadjuvant chemotherapy**

The safety evaluation indicators for the patients enrolled in the study should be immediately filled out by the investigators before the first cycle and after each cycle of neoadjuvant chemotherapy, with specific items including:

- Performance Status
- Subjective and objective status (according to records of CTCAE v3.0)
- Blood tests:
    - Peripheral venous blood assessment: WBC, Hb, PLT
    - Blood biochemistry: albumin, Na, K, total bilirubin, AST, ALT, creatinine Serum tumor markers: CEA, CA19-9, CA72-4

Safety evaluation items to be implemented during chemotherapy when necessary (refer to CTCAE v3.0):

- Neurotoxicity
- Cardiac toxicity
- Bone marrow suppression and infections due to immune dysfunction
- Others

**7. Preoperative Management**

- Surgical treatment should be performed within 1 week (including the 7th day) after randomization.
- Patients with nutritional risk are allowed to receive enteral/parenteral nutrition support before surgery.
- For high-risk patients of advanced age, smoking, diabetes, obesity, chronic cardiovascular or cerebrovascular thrombosis, etc, prophylactic measures, such as perioperative low molecular heparin, lower extremity antithrombotic elastic pants, active lower extremity massage, and respiratory function training, will be used. Other potential high-risk complications are determined by the investigator based on clinical practice and specific needs and must be detailed in the case report form.
- The patient will be fasted 1 day before surgery and water is forbidden 4 hours before surgery.

- Patients are not routinely placed with gastrointestinal decompression before surgery, except those with gastrointestinal obstruction.
- Prophylactic antibiotics during the perioperative period will be used in accordance with relevant national regulations.

## 8. Surgical treatment

### 8.1. Surgical approach

- Group A: laparoscopic distal gastrectomy with D2 lymphadenectomy.
- Group B: open distal gastrectomy with D2 lymphadenectomy.

### 8.2. Extension of gastrectomy

The extension of gastrectomy is performed in accordance with the Japanese Gastric Cancer Treatment Guidelines (3rd Edition). More than 2/3 of the stomach tissue at the distal end was removed. The proximal margin is at least 5 cm from the edge of the lesion, and there should be no tumor infiltration within 1 cm of the margin; the distal margin is located in the duodenal bulb and should be at least 3 cm from the edge of the tumor.

### 8.3. Extension of lymphadenectomy

According to the Japanese Gastric Cancer Treatment Guidelines (3rd Edition), D2 lymph node dissection should be performed. The dissection range includes No. 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, and 12a lymph nodes.

### 8.4. Digestive tract reconstruction

The way the digestive tract is reconstructed is determined by the surgeon based on his or her own experience and the specific circumstances of the operation, and can be selected from the standard anastomosis manners of Billroth-I, Billroth-II and Roux-en-Y.

### 8.5. Measures to prevent intraoperative complications

After the preoperative treatment, patient local tissue often has edema reaction, which may affect the tissue healing ability. According to the intraoperative situation, it is recommended to place local drainage on both sides of the anastomosis.

### 8.6. Quality control of surgery

For the purposes of quality control, the unedited full operation videos of patients undergoing laparoscopic surgery (Group A) and the photographs of lymph node dissection fields, surgical incisions, and specimen of patients undergoing open surgery (Group B) will be preserved. The specific requirements for the photographs are as follows:

- Lymph node dissection surgical field:

- Area under the pylorus, which must include the disconnection part of the right gastroepiploic artery and vein;
- The disconnection part of the left gastroepiploic vessels;
- The right side of the upper edge of the pancreas, which must include the anterior superior part of the common hepatic artery, 1/2 inward of the proper hepatic artery, and the disconnection parts of the right gastric artery;
- The left side of the upper edge of the pancreas, which must include the disconnection parts of the left gastric artery and vein, the celiac trunk, and the proximal part of the splenic artery;
- The right side of the cardia and small curvature of the residual stomach.
- After the skin incision is closed (with the ruler as the reference)
- Postoperative specimens (with the ruler as the reference):
    - Before dissecting the specimen, mark the lesion, the proximal and distal margins;
    - After dissecting the specimen, mark the lesion, the proximal and distal margins;

**8.7. Requirements of laparoscopic gastrectomy**

- Peumoperitoneum: using carbon dioxide pneumoperitoneum, maintaining a pressure of 12-13mmHg;
- Intra-abdominal procedures must be performed with the support of a camera system using a laparoscopic instrument;
- Gastric peripheral free, omental resection, retinal sac resection, lymph node dissection, and vascular management should be performed under laparoscopy;
- Gastric resection, digestive tract reconstruction can be done at the discretion of the surgeon, either under the laparoscope or through an auxiliary incision.

**8.8. Indications of conversion to open gastrectomy**

For those who underwent laparoscopic gastrectomy, the case is required to be converted to open surgery if one of the following happens: confluent lymph nodes with long axis >3cm, severe or life-threatening intraoperative complications such as intra-abdominal massive haemorrhage, severe organ damage, or other technical or instrumental factors that require conversion to open surgery.

**8.9. Observation items during surgery**

- Operation time, surgical approach, lymph node dissection range, digestive tract reconstruction method;

- Incision length, whether converted to open gastrectomy and why, the amount of blood loss, the amount of blood transfusion;
- Tumor location, size (maximum diameter), existence of distant metastasis, distal and proximal margin;
- The lactic acid value of arterial blood right before and after operation
- Intraoperative complications, including:
    - Surgical Complications: intraoperative injuries, including injuries to important organs and structures, or additional blood loss caused by vascular damage;
    - Gas-abdominal related complications: hypercarbia, mediastinal emphysema, subcutaneous emphysema, air embolism, respiratory circulation disorders caused by gas abdominal pressure;
    - Anesthesia-related complications;
- Intraoperative death (of all causes).

**9. Postoperative Management (same for both groups)**

**9.1. Use of Analgesics**

Postoperative pain control consists of patient-controlled analgesia (PCA), which is monitored daily by an anesthesiologist. PCA pumps will remain in situ for a maximum of three days.

**9.2. Fluid Replacement and Nutritional Support**

- Postoperative fluid infusion (including glucose, insulin, electrolytes, vitamins, etc.) or nutritional support (enteral/parenteral) will be performed based on experience and routine clinical practices, and is not specified in this study.
- After oral feeding, it is allowable to stop or gradually reduce fluid infusion/nutritional support.

**9.3. Postoperative Rehabilitation Management**

- Eating recovery time, diet transition strategies and management of drainage tube: Follow a standardized clinical pathway based on the Japanese Gastric Cancer Treatment Guidelines.
- Patients are encouraged to be out of bed and walking around the ward, under the guidance of a nurse.

**9.4. Patient Discharge Standards**

Discharge is recommended when the patients have tolerated more than 2days of soft diet without abdominal pain or fever. A delay in discharge due to 'non-medical' reasons will be recorded.

### 9.5. Postoperative Observation Items

- The pathology related records shall be completed within 2 weeks after the operation, including at least:
  - Radical resection of surgery (R0/R1/R2);
  - Histological type of primary lesion, Lauren type, and degree of differentiation;
  - Depth of invasion, number of lymph node dissection, number of lymph node metastasis;
  - Vascular thrombosis, nerve invasion;
  - Efficacy evaluation, using tumor regression grading (TRG) standard
- Postoperative complications within 30 days after operation (described in Section 5.2)
- Postoperative recovery (described in Section 5.2)

## 10. Postoperative Adjuvant Therapy

### 10.1. Indications for Postoperative Adjuvant Chemotherapy

After the surgical treatment is completed, all patients should receive postoperative adjuvant chemotherapy.

### 10.2. Postoperative Adjuvant Chemotherapy Program

Patients should start adjuvant chemotherapy within 6 weeks after surgery. Patients will receive the regimen same as neoadjuvant chemotherapy for 5 cycles. If oxaliplatin needs to be discontinued due to its specific toxicity (eg neurotoxicity), capecitabine should continue to be used for 6 months.

### 10.3. Safety Evaluation Indicators of Postoperative Adjuvant Chemotherapy

Same as preoperative neoadjuvant chemotherapy. (described in Section 6.2)

## 11. Follow-up

### 11.1. Follow-up Period and Precautions

The follow-up period is till 3 years after surgery. Patients are followed up every 3 months in the first 2 years and every 6 months afterwards.

### 11.2. Examination Items during Follow-up

- Physical examination (height, weight, Karnofsky score, heart/lung/abdominal physical examination);

- Laboratory examinations (fasting blood should be taken; for hemodialysis patients, blood should be taken before dialysis), including:
  - Blood cell analysis should include at least: WBC, LYM, NEU, NEU%, RBC, Hb, PLT
  - Blood biochemical analysis should include at least: albumin, AST, ALT, total bilirubin, creatinine, urea nitrogen, fasting blood glucose, CRP
  - Serum tumor markers, including at least: CEA, CA199, CA724, CA242, CA125
- Tumor evaluation, including
  - Abdominal pelvic ultrasound (every 3 months)
  - Abdominal pelvic enhanced CT and/or MRI scans (every 6 months)
  - Digestive Tract Endoscopy (every 12 months)
  - Chest X ray (every 3 months)
- During the study treatment, if recurrence/metastasis is suspected, tumor evaluation should be carried out at any time (clinical examination, cervical lymph node ultrasound, pelvic ultrasound/CT, chest X-ray or chest CT/MRI and abdominal enhancement CT/MRI). Possible reoperation or/and further treatment should also be recorded in the Case Report Form.

## 12. Study Calendar

| | **STUDY PERIOD** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Enrolment** | **Allocation** | **Post-allocation** | | | | **Close-out** |
| **TIMEPOINT** | ***-15 to -17 weeks*** | **0** | ***1 week*** | ***4 weeks*** | ***Year 1*** | ***Year 2*** | ***Year 3*** |
| **ENROLMENT:** | | | | | | | |
| **Eligibility screen** | X | | | | | | |
| **Informed consent** | X | | | | | | |
| **Allocation** | | X | | | | | |
| **INTERVENTIONS:** | | | | | | | |
| ***Preoperative chemotherapy*** | X | | | | | | |
| ***Open gastrectomy*** | | | X | | | | |
| ***Laparoscopic gastrectomy*** | | | X | | | | |

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|---|---|---|---|---|---|---|---|
| **ASSESSMENTS:** | | | | | | | |
| ***Physical examination*** | X | | | | X | X | X |
| ***Laboratory tests*** | X | | | | X | X | X |
| ***Oncology assessment*** | X | | | | X | X | X |
| ***Surgical radicality*** | | | | X | | | |
| ***Postoperative morbidity*** | | | | X | | | |
| ***Postoperative mortality*** | | | | X | | | |
| ***Postoperative recovery*** | | | | X | | | |
| ***Life quality*** | | | | X | X | | |
| ***Survival status*** | | | | | X | X | X |

## 13. Statistical Analysis Plan

### 13.1. Definitions of Analytic Sets

- Modified Intent-to-treat Population: Cases that underwent randomization and laparoscopic or open gastrectomy, with records of data of at least one valid efficacy evaluation after intervention.
- Per-protocol Population: Cases complying with the study protocol, with good compliance and completed Case Report Form, allowing statistical analysis of efficacy.
- As-treated Population: Cases that received laparoscopic or open gastrectomy and those who switched to the other group's approach are seen as the participants of the after-switch group.

### 13.2. Analysis principles

- Intention-to-treat and per-protocol approach will be used for efficacy analysis. As-treated analysis will be applied for safety analysis.
- For variables with a significant amount of missingness (>5%), multiple imputations will be conducted for the purpose of sensitivity analysis.
- For the primary analysis of recurrence-free survival, non-inferiority analysis will be used with a one-sided 97.5% confidence interval.
- All the other analyses will be superiority tests with two-sided 95% confidence interval and a type I error of 5%.

- Subgroup analyses will be carried out irrespective of whether there is a significant treatment effect on the primary outcome.
- Analyses will be conducted primarily using standard statistical software.

### 13.3. Analysis of Primary Endpoints

The non-inferiority test for the primary outcome of 3-year recurrence-free survival will be conducted by comparing the hazard ratio and its one-sided 97.5%CI with the critical value and non-inferiority margin, respectively. Survival rate will be estimated with Kaplan-Meier Method and compared by Log-rank tests. Hazard ratio will be generated by Cox Proportional Hazards Model.

### 13.4. Analysis of Secondary Endpoints

For the secondary outcome of 3-year overall survival, survival rate will be estimated with Kaplan-Meier Method and compared by a Log-rank test. Hazard ratio will be generated by Cox Proportional Hazards Models.

All the other categorical secondary outcomes be presented as number and percentage, and will be preferably analysed by a Chi-square test. A Fisher's Exact test will be used if the expected number within one cell is ≤5. Continuous outcomes will be presented as mean and standard deviation if normally distributed, or as median and interquartile range otherwise. Continuous outcomes will be preferably analysed by Student's t test or Wilcoxon rank-sum test.

### 13.5 Data Monitoring and Interim Analysis

Data monitoring and auditing are conducted by the funding agency annually. An interim analysis will be performed by an independent statistician when half of the patients have been randomised. The trial will be stopped if one treatment is found to be statistically more beneficial or harmful than the other.

## 14. Adverse Events

### 14.1. Definitions

AEs are any unfavourable or unintended events that affect the patients of the study, regardless of the relevance to the treatment. Events are defined as serious adverse events (SAEs) if they lead to death, prolongation of hospitalization, permanent or severe disability, teratogenesis or carcinogenesis, and significant clinical sequela.

### 14.2. Reporting of Adverse Events

Any AEs are recorded in detail on the case report form (CRF) and include time of occurrence, duration, relevance to the treatment, stopping or continuing of the treatment, and others. When a SAE occurs, it will be reported to Peking University Cancer Hospital Ethics Committee within 24 hours of the initial discovery.

## 15. Ethical Considerations

### 15.1. Responsibilities of Investigators

The investigators will ensure the implementation of this study in accordance with the study protocol and in compliance with the Declaration of Helsinki, as well as domestic and international ethical guiding principles and applicable regulatory requirements. It is specially noted that, the investigators must ensure that only subjects providing informed consent can be enrolled in this study.

### 15.2. Information and Informed Consent of Subjects

An unconditional prerequisite for subjects to participate in this study is his/her written informed consent. The written informed consent of subjects participating in this study must be given before study-related activities are conducted. The informed consent form must be signed and dated personally by the subjects and investigators. At any time, if important new information becomes available that may be related to the consent of the subjects, the investigators will revise the information pages and any other written information which must be submitted to the Institutional Review Board for review and approval. The revised information approved will be provided to each subject participating the study. The researchers will explain the changes made to the previous version of Informed Consent Form to the subjects.

### 15.3. Identity and Privacy of Subjects

After obtaining an informed consent form, each selected subject is assigned a subject ID. This number will represent the identity of the subject during the entire study and for the clinical research database of the study. The collected data of subjects in the study will be stored in the ID.

Throughout the entire study, only the investigators will be able to link to the research data of the subjects to themselves after authorization. The original medical information of subjects will be kept strictly confidential.

Collection, transmission, handling and storage of data on study subjects will comply with the data protection and privacy regulations. This information will be provided to the study

subjects when their informed consent is being obtained for treatment procedures in accordance with national regulations.

### 15.4. Independent Ethics Committee or Institutional Review Committee

Before beginning the study at the center, the written proof of favorable opinions/approval by the Institutional Review Board must be obtained. In case of major revisions to this study, the amendment of the study protocol will be submitted to the Institutional Review Board prior to performing the study. In the course of the study, the relevant safety information will be submitted to the Institutional Review Board in accordance with national regulations and requirements.

## 16. References


1. Jemal, A., et al., Cancer statistics, 2010. CA Cancer J Clin, 2010. 60(5): p. 277-300.

2. Ferlay, J., et al., Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer, 2010. 127(12): p. 2893-917.

3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011 Jun;14(2):113-23. doi: 10.1007/s10120-011-0042-4.

4. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355(1):11-20. doi: 10.1056/NEJMoa055531

5. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29(13):1715-21. doi: 10.1200/JCO.2010.33.0597

6. Qiu J, Pankaj P, Jiang H, et al. Laparoscopy versus open distal gastrectomy for advanced gastric cancer: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2013;23(1):1-7. doi: 10.1097/SLE.0b013e3182747af7

7. Yoshikawa T, Fukunaga T, Taguri M, et al. Laparoscopic or open distal gastrectomy after neoadjuvant chemotherapy for operable gastric cancer, a randomized Phase II trial (LANDSCOPE trial). Jpn J Clin Oncol 2012;42(7):654-7. doi: 10.1093/jjco/hys057

8. Neuenschwander B, Rouyrre N, Hollaender N, et al. A proof of concept phase II non-inferiority criterion. Stat Med 2011;30:1618–27.

## 17. Annex

### 17.1. Informed Consent Form

**Informed Consent Form**

Study name：A Comparison of Laparoscopic With Open Distal Gastrectomy in Advanced Gastric Cancer After Neoadjuvant Chemotherapy

Protocol version：2.0, 2015 February 26

Informed consent form version：2.0, 2015 February 26

Research institute：Peking University Cancer Hospital

Patient name： Patient initials：

Patient address：

Patient phone number：

We invite you to participate in a clinical trial. This informed consent form provides you with some information to help you decide whether to participate in this clinical trial. Please read the following carefully, if you have unclear questions or terminology, please feel free to discuss with the reception physician.

Your participation in this study is entirely voluntary. The current study has been reviewed and approved by the Beijing Cancer Hospital Ethics Committee.

1. Research background

The purpose of this study was to provide a thorough evaluation of the safety and efficacy of laparoscopic radical gastrectomy for gastric cancer patients with neoadjuvant chemotherapy through a prospective, randomized, controlled, open-label, single-center phase II clinical study.

2. Research process:

You and your family will be informed the treatment results of this study. All data and information are confidential to people outside the study and will be used only for the purpose of this study.

Through initial abdominal/pelvic enhanced CT scan, endoscopy, etc., patients diagnosed with gastric cancer, with no clear abdominal implants, and judged feasible for radical resection, will be enrolled in the study after signing the informed consent form. Three-weeks

after the neoadjuvant chemotherapy, vital signs examinations, physical examinations, laboratory tests, 12-lead electrocardiograms in a calm state, respiratory function tests, and oncological evaluations (same categories as the screening tests) again, will be again performed to evaluate the resectability of the surgery. Resectable patients will be randomly assigned to the laparoscopic-assisted distal gastrectomy or open gastric radical gastrectomy groups. Follow-up period begins from the end of the study treatment to 3 years after the operation. Follow-up will be conducted every 3 months within the first 3 years and every 6 years in the last year. At the end of the follow-up period, statistical analysis will be performed on the patient data to obtain the final conclusion of the study. In addition, you will need to fill in the quality of life questionnaire so that we can understand your quality of life in a timely manner.

3. Risk and discomfort of participating in the study:

The risk of this project is mainly focused on adverse events as follows:

The complications associated with laparoscopic exploration include: laparoscopic surgery related risk, such as hypercapnia, hypoxemia, and bowel injury during the exploration. However, according to the previous experience of our department, the probability of bowel injury is extremely low, and can be found and dealt with accordingly in the exploration process.

Perioperative chemotherapy related adverse events: bone marrow suppression, gastrointestinal reactions, liver and kidney dysfunction, malnutrition, severe allergic reactions, peripheral neuritis,etc. MAGIC and other studies have confirmed that neoadjuvant chemotherapy did not cause additional serious side effects compared to surgery alone.

In addition, patients may experience anesthesia and surgical related discomfort including wound pain, postoperative fever, gastrointestinal discomfort after abdominal surgery including abdominal distension, abdominal pain, acid reflux, nausea, etc. A small number of patients may experience postoperative complications of radical gastrectomy including anastomotic leakage and bleeding. Most patients' condition will be relieved after conservative treatment. A very small number of patients have the possibility of worsening disease, loss of surgical opportunities, and loss of opportunities for radical cure.

4. Benefits of participating in the study:

If you agree to participate in this study, you may or may not have direct medical benefits. Patients in this study will receive a standardized diagnosis and treatment of gastric cancer.

Through diagnostic laparoscopic exploration, occult peritoneal metastases will be excluded, which avoids the lack of treatment or over-treatment due to inaccurate staging to the greatest extent. Some patients may benefit from a comprehensive treatment model with perioperative chemotherapy, which increases surgical radicalness, decreases local recurrence possibility, and improves overall survival.

5. Alternative treatment:

In addition to participating in this study, you have the following options: laparotomy, radical gastrectomy

6. Costs of participating in the study: None.

7. The right to refuse to participate in or withdraw from the study:

You may choose not to participate in this study, and have the right to withdraw without any reason at any stage of the trial. Such a decision will not affect any of your medical treatment or rights. Once you have decided to participate in this study, please sign this informed consent form. Before entering the study, the doctor will evaluate your eligibility of participation.

If you choose to participate in this study, we hope you will continue to complete the entire research process.

8. Privacy and confidentiality issues:

During the research period, your personal data such as your name, gender, etc. will be replaced with a code or number and strictly confidential. Only the relevant doctors will know your information and your privacy will be well protected. The results of the study may be published in academic journals but will not reveal any of your personal data.

If you agree to participate in this study, all your medical data will be screened by relevant personnel of the organization that initiated the study, relevant authorities, or an independent ethics committee, to check the appropriateness of the study's implementation. If you sign this informed consent form, it means that you agree to receive the above persons' review.

9. Medical cost reduction

Due to the need of this trial, laparoscopic exploration is required before the laparoscopic or open gastrectomy, and the use of an ultrasonic scalpel is required for the purpose of

research treatment. Therefore, the current study provides partial cost reduction for participating patients.

| Item | Cost (Yuan) | Frequency | Total cost （Yuan） |
|---|---|---|---|
| ultrasonic scalpel | 600 | 1 | 1,600 |
| Laparoscopic surgery | 1,000 | 1 | |

How to get help in the study:

You can have access to the information and research progress related to this study at any time point. If you have any questions related to this study, please feel free to contact Dr. Li Ziyi at 010-88196606.

If you need to know about the rights of participating in this study during the research process, you can contact the Ethics Committee of Beijing Cancer Hospital at 010-88196391.

**Informed consent form—Signature page**

If you fully understand the content of this research project and agree to participate in the study, you will need to sign this informed consent, in two copies, to be retained by the researcher and by you.

Research topic：

Signatory：

Declaration of Consent：

1、 I have confirmed that I have read and understood the informed consent of this study, that the problems and solutions which may arise during the course of the study have been explained to me, and that I have had the opportunity to raise my own questions.

2、 I have known that participation in the study is entirely voluntarily and refusing to participate will not jeopardize any of my interests.

3、 I have learned that the physicians involved in this study, the hospital manager of this study, and the Ethics Committee have the right to review the research records and case data, and I agree that these people will have access to my research records and understand that the above information will be treated confidentially.

4、 I agree to participate in this study.

Full name of patient name：

Date:

Full name of the legal representative： Date:

Completed by the reception physician:

The researcher statement: I confirm that the patient has been explained and discussed about the nature, purpose, requirements and possible risks of the study, as well as other alternative treatment options, and that a copy of the subject's information has been given to the patient for preservation.

Full name of the researcher：

Date: